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NARRATIVE REVIEW

Challenges for a broad international implementation of the current severe community-acquired pneumonia guidelines

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Abstract

Severe community-acquired pneumonia (sCAP) remains one of the leading causes of admission to the intensive care unit, thus consuming a large share of resources and is associated with high mortality rates worldwide. The evidence generated by clinical studies in the last decade was translated into recommendations according to the first published guidelines focusing on severe community-acquired pneumonia. Despite the advances proposed by the present guidelines, several challenges preclude the prompt implementation of these diagnostic and therapeutic measures. The present article discusses the challenges for the broad implementation of the sCAP guidelines and proposes solutions when applicable.

Keywords: Severe community-acquired pneumonia, ICU, Acute respiratory failure, Sepsis, Lower respiratory tract infection, Guidelines

Introduction

Severe community-acquired pneumonia (sCAP) remains one of the significant causes of admission to the intensive care unit (ICU) both in high and low- and-middle-income countries (LMICs) [1]. In the past 3 decades, advances both in the management of sepsis, respiratory failure, and general management of ICU patients reduced the burden of organ dysfunctions and decreased the rates of ICU-acquired complications, resulting in improved overall survival rates [1].

Despite these advances, CAP remains among the top five causes of mortality worldwide (1). Therefore, a set of specialized, updated, evidence-based recommendations for its management was published in the recent guidelines [2].

In the present article, we discuss the challenges to a broad implementation of the current guidelines and, when appropriate, propose potential solutions to overcome barriers and increase adoption.

The use of molecular diagnosis in severe CAP

The first recommendation in the guidelines states: 'If the technology is available, we suggest sending a lower respiratory tract sample (either sputum or endotracheal aspirates) for multiplex polymerase chain reaction (PCR) testing (virus and/or bacterial detection) whenever non-standard sCAP antibiotics are prescribed or considered.' It is a conditional recommendation based on very low-quality evidence [2]. The rationale for suggesting multiplex PCR testing in routine practice is the ability to rapidly identify pathogens and adjust antibiotics,

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especially for unsuspected antibiotic-resistant pathogens. The lag time for traditional microbiological results is a 48- to 72-h interval, and a delay in adjusting therapy is associated with adverse outcomes in CAP. There are also potential harms, including excess drug toxicity at the individual level and an increased risk of antibiotic-resistant infections due to resistance selection/emergence pressure [2, 3].

Multiplex PCR techniques have several issues due to their limited accuracy. Although high sensitivity is described in several studies, the high risk of inappropriate escalation of antibiotics based on false-positive PCR results is well known [4]. In addition, prospective evaluation of interventions/protocols based on PCR multiplex results is limited. Still, the cost-effectiveness analysis benefits are yet to be proven, as the costs associated with platform implementation and consumables might exceed those of empirical therapy and/or healthcare in a hospital setting.

Considering the application of this recommendation in LMICs, the coronavirus disease 2019 (COVID-19) pandemic positively affected the infrastructure implementation of molecular biology facilities worldwide due to the necessity to test most of the population and improvements in healthcare personnel training. We have improved the ability to detect viruses as the primary cause of respiratory infection [5], with well-described epidemiological and therapeutic consequences [6].

However, some important concerns remain in this setting. A golden rule for building laboratory capacity in resource-limited settings is selecting workable techniques that can be sustained [6]. It is unclear whether this infrastructure will remain available or can be promptly mobilized to start testing other platforms in the long term. In addition, the long-term availability of trained personnel and access to the test in routine, outside of a pandemic scenario, is still being determined. As stated, 'PCR is easy to do badly,' and the likelihood of waste, contamination, or data [6, 7] misinterpretations from poorly executed molecular tests is a significant concern. Still, limited resources need to be redirected to the implementation/maintenance of infrastructure/personnel for molecular biology facilities without a clear benefit yet demonstrated [6, 8].

Despite these difficulties, however, it is time to address the issue of strengthening clinical bacteriology in low-resource settings [9], and the provocative nature of this recommendation can be valuable. The benefits of clinical bacteriology are numerous, not only for individual patient care, and the deployment of Gene Xpert for the detection of tuberculosis in resource-constrained settings and the increase in capacity during the severe acute respiratory syndrome coronavirus 2 pandemic are good examples of the feasibility to adopt innovative molecular technologies to improve healthcare. We have, however, to acknowledge that there is a need to determine the implementation of molecular diagnosis if conventional microbiology and clinical bacteriology are not available in many settings. Moreover, multidrug-resistant (MDR) pathogens would be expected when risk factors are present or predictive scores; however, such factors or scores were studied mostly in high-income countries settings. Their validity in LMICs (where the prevalence of MDR in sCAP is largely unknown, which should directly affect predictive performance of these variables) is still undetermined.

Take-home message

The first guidelines of community-acquired pneumonia with a severe presentation represent a significant advance for the management of patients. However, there are still several challenges to its broad implementation, namely related to external validation, availability of resources, and the need for setting adaptation of recommendations that must be addressed both at the time of performance and in future studies.

NIV and HFNC in the management of severe community-acquired pneumonia

Acute hypoxemic respiratory failure (AHRF) during severe CAP is frequently associated with strong inspiratory efforts. This can aggravate the underlying lung injury due to the high transpulmonary pressures generated and the heterogeneity of lung inflation (patient self-inflicted lung injury). In addition to improving oxygenation and enhancing comfort, noninvasive respiratory supportive therapies should relieve inspiratory muscles' workload. Noninvasive ventilation (NIV) or continuous positive airway pressure (CPAP) through a face mask or helmet and high-flow nasal cannula oxygen therapy (HFNC) have been proposed in this setting, as they can provide high levels of inspired oxygen and decrease the work of breathing. The current section reflects the available literature where most randomized controlled trials (RCT) were performed in specific populations, immunosuppressed and COVID-19 patients, and not in a heterogeneous sCAP cohort with diverse etiologies.

Since the 2000s, many studies comparing NIV with conventional oxygen therapy (COT) have reported conflicting results for intubation or mortality [10]. Moreover, two recent randomized clinical trials in immunosuppressed patients reported no significant differences between NIV and COT or NIV and HFNC (Table 1) [11, 12]. In a first single-center trial in acute respiratory distress syndrome (ARDS) patients in 2016, helmet NIV showed superiority over facemask NIV regarding intubation and mortality.

Table 1 Main randomized clinical trials comparing oxygen support

Sources	Total number of patients	Main reasons for hypoxemic respiratory failure	Oxygen strategies	PaO_2/FiO_2	Respiratory rate	Main results	Comments
NIV							
Lemiale et al. (2015)	374	Immunosuppression with ARF	Standard vs. O_2NIV	156 mmHg	25 and 27/min	No difference in 28-day mortality and intubation rates: 28-d mortality, 24 vs. 27% Intubation, 38 vs. 45%	38% of patients received HFNC in both groups NIV: Vt 8.8 ml/kg of PBW
DCoudroy et al (2022)	299	Immunosuppression with ARF	NIV vs. HFNC	147 mmHg	31 and 32/min	No difference in 28-day mortality and intubation rates: 90-d mortality, 35 vs. 36% Intubation, 45 vs. 51%	NIV settings: PS 7 and PEEP 7 cmH_2O, Vt 9.6 ml/kg of PBW HFNC: 58 L/min
Helmet-NIV							
Patel et al (2016)	83	ARDS	NIV mask vs. NIV helmet	144 and 118 mmHg	–	Reduction of intubation and mortality rates with NIV helmet: Mortality 90-d, 56 vs. 34% Intubation, 61 vs. 18%	Half of the patients were immunocompromised 456 patients were excluded because they received NIV < 8 h before randomization Trial stopped after first intermediate analysis NIV mask: PS 11 and PEEP 5 cmH_2O NIV helmet: PS 8 and PEEP 8 cmH_2O External validity: very high intubation and mortality rates in NIV mask group
Grieco et al (2022)	109	Respiratory failure due to COVID-19	HFNC vs. NIV helmet	102 mmHg	28/min in both groups	Reduction of intubation rate with NIV helmet: Intubation, 30 vs. 51% 28-d mortality, 15 vs. 18%	20% of intolerance in NIV helmet group
Arabi et al	320	Respiratory failure due to COVID-19	Usual care vs. NIV helmet	73 and 76 mmHg	–	No difference in ICU-mortality and intubation: Intubation, 47 vs. 50% ICU-mortality, 35 vs. 37%	Usual care: 76% of patients receive HFNC during 13 h/day NIV helmet: 36% of patients discontinued for intolerance

Table 1 (continued)

Sources	Total number of patients	Main reasons for hypoxemic respiratory failure	Oxygen strategies	PaO_2/FiO_2	Respiratory rate	Main results	Comments
HFNC							
Frat et al (2015)	310	Hypoxemic ARF	Standard O_2 vs. HFNC vs. NIV	161, 157 and 149 mmHg	32, 33 and 33/min	Reduction of mortality rate with HFNC, but not of intubation rate: intubation, 44 vs. 38 vs. 50% Mortality 90-d, 23 vs. 12 vs. 28%	HFNC: 48 L/min NIV: PS 8 and PEEP 5 cmH_2O Post hoc analysis in severe patients (238 of 310 patients: decreased intubation and mortality rates in HFNC group
Azoulay et al (2018)	776	Immunosuppression with ARF	Standard O_2 vs. HFNC	128 and 136 mmHg	32 and 33 /min	No difference in ICU mortality and intubation: intubation, 44 vs. 39% Mortality, 36% in both groups	81/776 (10%) patients had more than 10 L/min of oxygen at randomization 40% of patients deceased without being intubated in HFNC group
Perkins et al (2022)	1273	Respiratory failure due to COVID-19	Standard O_2 vs. HFNC standard O_2 vs. CPAP	76, 75, 89 mmHg in standard O_2, HFNC, CPAP group, respectively	O_2 standard, HFNC, CPAP, respectively: 30, 28, and 34/min	No difference between standard O_2 and HFNC in intubation and mortality Benefit of CPAP vs. standard O_2 in intubation	No predetermined criteria of intubation Trial recruitment was stopped early due to a rapid decline in hospitalized patients with COVID-19 in the UK Subgroups analyses: in patients with a $FiO_2 > 0.6$, HFNC was associated with a decreased intubation risk
Ospina-Tascon et al (2022)	199	Respiratory failure due to COVID-19	Standard O_2 vs. HFNC	73 and 78 mmHg	28 and 28/min	Reduction of intubation rate with HFNC, but not of mortality rate: intubation, 51 vs. 34% Mortality 28-d, 16 vs. 8%	HFNC decreased the time to clinical recovery More VFD-28 in HFNC group
Frat et al (2022)	711	Respiratory failure due to COVID-19	Standard O_2 vs. HFNC	132 and 128 mmHg	29 and 28/min	Primary outcome: mortality 28-d, 11 vs. 10% Secondary outcome: reduction of intubation rate with HFNC: intubation, 53 vs. 45%	No differences in VFD-28 After 1 h of treatment onset: *Lower PaO_2/FiO_2 in HFNC group *Lower respiratory rate in HFNC group

ARDS, acute respiratory distress syndrome; *ARF*, acute respiratory failure; *COVID-19* coronavirus disease 2019; *CPAP* continuous positive airway pressure; *HFNC*, high-flow nasal oxygen therapy; *ICU* intensive care unit; *NIV*, noninvasive ventilation through mask; *PBW*, predicted body weight; *PEEP*, positive end-expiratory pressure; *PS*, pressure support; *UK* United Kindom; *VFD-28*, ventilator-free days at day 28; *Vt* tidal volume

However, in COVID-19 patients, helmet NIV showed conflicting results compared to HFNC (Table 1) [13, 14]. Therefore, there is no strong evidence for using facemask NIV or helmet in severe pneumonia, even when caused by COVID-19. However, it is unknown whether NIV might benefit patients when its use is associated with decreased inspiratory efforts.

In contrast, as compared to COT, CPAP has been associated with a lower risk of intubation in COVID-19 patients [15]. It is essential to consider that most of the present evidence comes from studies on COVID-19. Therefore, their results may not be directly extrapolated to patients with sCAP of other etiologies.

The benefits of HFNC in patients with AHRF were reported in an initial trial in 2015, which showed decreased mortality and intubation rates in more severely hypoxemic patients compared to COT and NIV [16]. However, these results were not confirmed in another large-scale trial comparing HFNC with COT in immunosuppressed patients [17] (Table 1). In patients having AHRF due to COVID-19, two trials showed decreased intubation rates with HFNC as compared to COT [18], while another study showed benefits of HFNC only in severe patients [15, 19] (Table 1). Therefore, compared with COT, HFNC seems beneficial regarding intubation, while its effect on mortality seems uncertain.

Challenges to a broad implementation go beyond the potential controversies and uncertainties in the literature. It is fundamental to individually evaluate the ICU and the setting to ensure the availability of resources (i.e., helmets, facemasks, cannulas, ventilators), designing an evidence-based protocol, adequate training of the team regarding criteria to start and interrupt NIV/HFNC as well as the proper monitoring of patients to detect a failure at an early stage. Regarding HFNC, consequence of the huge oxygen consumption poses an additional challenge due to the need of an optimized oxygen supply chain.

Implementing the recommendation for macrolides in patients with severe CAP

Recent clinical guidelines recommend a combination therapy of beta-lactamase-based regimen and macrolides for treating patients with sCAP. Observational studies support this regimen, showing reduced 30-day mortality, decreased need for invasive ventilation, and long-term mortality reduction [20–23]. However, implementing these recommendations poses challenges, especially in countries with limited macrolide access due to availability or regulations. LMICs face additional constraints, such as limited healthcare infrastructure, funding, and drug availability, hindering macrolide adoption. In addition, more evidence is needed to separate the anti-inflammatory from the antimicrobial effects. This is even more important in regions (or patients) where the rates of atypical pathogens are lower.

Also, antimicrobial resistance further complicates implementation, especially in areas with high macrolide resistance rates. To address this, robust surveillance programs and appropriate antibiotic stewardship practices are vital [24, 25].

Effective implementation of macrolide recommendations relies on raising awareness and educating healthcare providers, patients, and stakeholders. Thus, tailored educational initiatives and awareness campaigns must ensure guideline adherence across different cultural and linguistic contexts [26]. Therefore, it is essential to accurately translate and adapt guidelines to local contexts, considering cultural beliefs/data and practices. Failure to address these barriers may lead to misinterpretation or ineffective recommendations application.

In conclusion, the broad international implementation of macrolide recommendations in sCAP guidelines faces numerous challenges. To overcome these challenges and convince prescribers and payers to adopt macrolides in the empirical treatment of patients with sCAP globally, it is crucial to address regional variations, resource constraints, antibiotic resistance concerns, evidence-based limitations, awareness and education gaps, and foster collaborative efforts to generate high-quality data. In addition, areas of uncertainty need further research, such as determining the preferred macrolide, optimal treatment duration, and the sequence of starting macrolides before or after the beta-lactam antibiotic [27]. By addressing these challenges and bridging the gaps in the literature, healthcare systems can enhance the quality of care provided to patients with severe CAP worldwide.

The use of systemic corticosteroids for sCAP

The guidelines for the treatment of sCAP recommend the use of corticosteroids if shock is present. Considering more recent data and data analysis, we recommend that corticosteroids for sCAP should not be based solely on the presence of shock rather, adjuvant corticosteroids should be considered in selected cases in which the clinician deems that an individual patient is at an exceedingly high risk of death. A patient-level meta-analysis in adults with septic shock showed no benefit of adjuvant corticosteroids in patients with concomitant pneumonia (1701 patients analyzed; risk ratio (RR) 0.92 [95% confidence interval (CI) 0.79–1.05]) [28].

The CAPE COD trial included $N=795$ patients with sCAP and no shock at baseline and found a 5.6% absolute reduction in 28-day mortality (95% CI −9.6 to −1.7) with corticosteroid therapy [29]. Nonetheless, these results are in stark contrast to another large ($N=584$ patients) RCT (ESCAPE) of patients admitted to the ICU for sCAP in whom corticosteroid did not result in improved 60-day

mortality (16% vs. 18%; adjusted odds ratio 0.90, 95% CI 0.57–1.40) [30].

The aggregate of data from RTCs does not support either the use of adjuvant corticosteroid therapy for all patients with sCAP (defined as patients admitted to the ICU) or for the subset of patients with septic shock. Instead, the evidence suggests that corticosteroids were more likely to be beneficial in trials where the study patient population demonstrated some features (e.g., high PSI or CURB 65) indicating severe disease and increased risk of death [31]. There is neither a single clinical marker, including the presence of shock, nor a single clinical scoring system that dependably identifies patients with sCAP at high risk of death who would benefit from corticosteroid therapy. Besides, its use is associated with several adverse events like hyperglycemia and nosocomial infections that constitute an additional challenge in low-resource settings. Despite the weakness of the current evidence, we suggest that corticosteroids may be used in selected patients with sCAP, are not previously immunocompromised, not infected with Influenza, and have severe respiratory failure requiring high-flow, noninvasive or invasive ventilation and/or refractory septic shock, which the treating physician deems to be at exceedingly high risk of death based on clinical, radiologic, and microbiologic evaluation.

Procalcitonin to guide antimicrobial therapy in sCAP

Biomarker-guided strategies use C-reactive protein (CRP) and procalcitonin (PCT) to tailor the duration of antibiotic therapy according to the individual response to treatment. Although no biomarker-guided RCTs for exclusively sCAP patients is available, PCT was the single biomarker addressed in the current guidelines citing previous trials on CAP and sepsis that included this population. Below, we briefly revise the literature and address some concerns about its broad implementation. The recommendations were based on three RCTs on critically ill patients (where sCAP was the main type of infection). In these trials, PCT-guided therapy was associated with a shorter duration of antibiotics but had no impact on ICU and hospital lenght of stay (LOS) or mortality. In addition, the duration of treatment on the PCT arm was not shorter than the duration currently recommended by guidelines. A recent systematic review and meta-analysis (SRMA) [32] demonstrated that using a PCT-guided strategy was not superior to a fixed duration of 5–7 days of antibiotic therapy. Thus, in settings with high compliance to short antibiotic courses, PCT is not an added value. However, a non-decreasing PCT per se should not be used to escalate antibiotics or intensify diagnostics. This strategy has no impact on survival and leads to longer multi-organ failure and longer antibiotic therapy [33].

Although it is important to distinguish between viral and bacterial etiologies and to identify co-infection in sCAP, an SRMA [34] showed that PCT is not useful for that purpose. Moreover, when incorporating PCT into practice, one should know that its concentration increases with a decrease in glomerular filtration rate and decreases during renal replacement therapy. Furthermore, a setting-adapted approach is needed because PCT-guided therapy implies daily measurements that are associated with increased costs. In a small single-center RCT [35] with critically ill patients with sepsis (not specifically sCAP), similar performance of PCT and CRP-guided therapy was found, suggesting the latter as a more accessible alternative.

Finally, it is paramount to mention that there is no data assessing the impact of PCT strategy on antibiotic consumption in the ICU. However, at a hospital level, the implementation of PCT was paradoxically associated with a significant increase in antibiotic consumption [36]. This means that PCT-guided therapy is not necessarily associated with less antibiotic pressure. This is especially relevant when we consider that a fixed treatment duration of 7 days, thus, shorter than in most studies "control arms" is effective for sCAP, even for ICU patients as stated in the guidelines.

The use of antivirals in the management of sCAP (influenza and beyond)

We have recently observed a rise in the detection of viral agents in sCAP either as an effect of the COVID-19 pandemic, the increased use of molecular testing or to other less well determined causes. The use of antivirals in the management of sCAP is often initiated empirically until the results of microbiological tests become available. Nevertheless, the increasing use of rapid molecular tests considerably reduces the time to results, potentially guiding antimicrobial use [37].

The decision to use an antiviral drug in sCAP is based on several factors, such as the clinical presentation, availability of specimens and assays, and finally, the season of the year. Considering that up to 30% of bacterial CAP may be co-infected with viral microorganisms [38], a proper and comprehensive assessment of clinical presentation including radiological findings (type and extent of findings), clinical signs and symptoms (severity of general and respiratory impairment), timeline of disease progression, and laboratory findings are all essential to decide on the most appropriate course of therapy.

The kind of samples available for the microbiological investigation will have implications in different aspects: for instance, time to results will differ, as well as sensitivity and specificity of microbiological tests (cultures, antigens, antibody/antigen-based tests, molecular tests)

depending on sample type and quality (sputum, bronchoalveolar lavage, nasal swab, blood, pleural fluid) Also, interpretations of results will depend on the sample being considered and patients' characteristics [39, 40].

The last and likely most relevant factor influencing the decision to include an antiviral in the antimicrobial treatment of sCAP is the prevalence of the most relevant respiratory viruses, such as influenza, SARS-CoV2, and respiratory syncytial virus (RSV), which tend to peak during winter seasons in all continents and current guidelines recommend the treatment with oseltamivir, for instance, during influenza season [2]. In the ICU, acute influenza infection should be suspected in patients with severe pneumonia, ARDS, and sepsis, particularly in the winter season. More recently, during the SARS-CoV2 pandemic, the use of new antivirals such as remdesivir has shown clinical and survival benefits in hospitalized patients [41, 42].

The empiric initial therapy of sCAP only should include other antivirals, such as inhaled ribavirin in selected cases of RSV pneumonia for patients with hematological diseases and intravenous ganciclovir or acyclovir in cases of cytomegalovirus or herpes simplex pneumonia, respectively, in immunocompromised patients, particularly in bone marrow and organ transplant recipients.

When to consider multidrug-resistant bacteria in sCAP?

The proportion of multidrug-resistant bacteria (MDRB), among those responsible for sCAP, has increased, especially among Enterobacterales [43]. To balance the risk of multidrug resistance and the benefit of appropriate initial antimicrobial treatment in sCAP, recent international guidelines suggest integrating specific risk factors (eventually computed into clinical scores) based on local epidemiology and previous colonization to guide decisions regarding drug-resistant pathogens (excluding those immunocompromised) and empirical antibiotic prescription in sCAP patients (conditional recommendation, moderate quality of evidence) [2].

The major challenge in the broad implementation of these guidelines is to consider local microbial resistance epidemiology, as in many individual institutions and countries, these data might not be available. Another important limitation is the lack of information on MDR risk factors in some patients, at least during the first 24 h of ICU admission, when it is crucial to give appropriate antimicrobial treatment.

The exclusion of immunocompromised patients from these guidelines is probably based on the general belief that these patients are at higher risk for infections related to MDRB. Previous international guidelines have even suggested that these patients should be classified at high risk for pneumonia related to MDRB and routinely treated with broad-spectrum antimicrobials [44]. However, to our knowledge, no data are available on the microbiology of sCAP in immunocompromised patients, and whether these patients are at higher risk for infections related to MDRB is unknown. Further, recent data suggest that immunocompromised patients are at lower risk for ICU-acquired colonization and infection by MDRB [45]. The definition of immunosuppression is not dichotomic and further research should be done to determine the type (innate or adaptive) acquisition (acquired or innate) and the degree of immunosuppression (mild, moderate, severe) affecting the patient.

Drug resistance has recently been classified into four categories in sCAP: pathogen acquisition related to healthcare exposure; colonization persistence (immunosuppression, chronic lung disease, history of colonization, or infection with MDRB); antibiotic-mediated selective pressure-promoting resistance; and factors altering host physiology (cognitive/neurological impairment, gastric acid suppression, etc.) [46]. Two observational studies suggested that using models to predict resistance in sCAP was associated with reduced use of broad-spectrum antimicrobials, while maintaining good outcomes [47, 48]. Further large prospective studies are required to validate this strategy. The rapid microbiologic techniques that could help in the identification of MDRB could be through the identification of resistance genes by multiplex PCR tests as well as through phenotypic antibiotic sensitivity testing. Both techniques if coupled with a good antimicrobial stewardship program are associated with a faster escalation and de-escalation of antibiotics. A potentially interesting alternative is the use of rapid microbiological techniques in patients with risk factors for MDR, to avoid unnecessary broad-spectrum antimicrobials in sCAP. This might allow targeting patients benefiting from these rapid techniques and reducing broad-spectrum antimicrobial use.

Aspiration pneumonia as a form of severe community-acquired pneumonia

Aspiration syndromes include aspiration pneumonia (AP), an infection caused by specific pathogens, and chemical pneumonitis (CP), an inflammatory response to aspirated gastric contents. AP accounts for up to 15% of CAP and is responsible for higher mortality rates than other forms of sCAP (29.4% vs. 11.6%) [49]. Traditionally, it has been debated to add an anti-anaerobic treatment, but due to the typical etiology, it seems not needed. Macro-aspiration of oropharyngeal or upper gastrointestinal contents may cause tissue injury with disruption of the lung microbiome and development of AP [50]. The main pathogens found in AP from patients admitted from the community are the same as in CAP, so *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus*

influenzae, and Enterobacteriaceae with anaerobes play a lesser role.

Risk factors for AP include impaired swallowing, decreased consciousness, and or cough reflex with multiple risks increasing rates of AP and death. Two or more risk factors are associated with increased rates of recurrent pneumonia and 30- and 60-day mortality [51]. In stroke patients, the use of an angiotensin-converting enzyme inhibitor was associated with a protective effect on AP [52].

Diagnosis relies on a history of macro-aspiration, findings of pulmonary infection, and the presence of risk factors. Chest radiographs may indicate an infiltrate in a gravity-dependent lung segment. In severe cases of macro-aspiration, early bronchoscopy may be considered to remove bronchial contents, although the level of evidence is weak [53].

Treatment of severe AP depends primarily on the risk of infection with a resistant or MDRs. If resistance is likely, a broad-spectrum regimen should be started with piperacillin–tazobactam, cefepime, levofloxacin, imipenem, or meropenem, either singly or in combination depending on local ecology and having a good anti-anaerobic spectrum [54].

In severe AP cases, antibiotics may be started initially, and their need and spectrum of activity reassessed after 48–72 h. If the patient fails to improve over 48 to 72 h or worsens, an aggressive workup to exclude necrotizing pneumonia, lung abscess, empyema, or an extrapulmonary focus is needed. Treatment duration is usually 5 to 7 days if there is a good clinical response.

International implementation: barriers and potential solutions

sCAP remains a major cause of mortality, especially in LMICs, where arguably the burden and impact of early and potentially preventable mortality is greatest. Here, in brief, we analyzed the potential barriers to a successful and broad implementation of the present guidelines (Table 2): (1) increases in the number of individuals susceptible to CAP and to developing sCAP; (2) low awareness of sCAP by patients, families, and healthcare professionals; (3) delayed access to adequate care; (4) low resource availability; and (5) suboptimal ICU organization and processes.

Considering the specific sCAP guidelines recommendations, we must consider costs, complexity, and availability or expertise to deliver the interventions. Moreover, as in any clinical practice guideline, cultural barriers to

Table 2 General barriers and potential solutions to increase effective and broad international implementation of sCAP guidelines

Problems/barriers	Category	Solutions
Increased population at risk for severe CAP		
Aging of population	Pre-hospital/non-modifiable	Better triage and referral at emergency department of high-risk patients
Increases in non-communicable diseases and burden of comorbidities	Pre-hospital/non-modifiable	Better triage at emergency department of high-risk patients
Increase immunosuppressed population	Pre-hospital/non-modifiable	Better triage at emergency department of high-risk patients
Low vaccination coverage of high-risk patients (i.e., influenza, pneumococcal)	Pre-hospital/modifiable	Vaccination campaigns (community) and post-hospital vaccination (for patients admitted due to CAP)
Low CAP awareness of families, patients, healthcare professionals	Pre-hospital/modifiable	Campaigns, education
Inequities in access and delays of care delivery		
Delays in recognition of potential severity and ICU admission	In-hospital/modifiable	Training of all healthcare workers, education, risk assessment tools
Delays/Lack of timely antibiotics and supportive care	In-Hospital/modifiable	Training, protocol implementation, Staff optimization, and empowerment
Specific guideline recommendations		
PCT to guide antimicrobials: unavailable; guideline overruling; costs	In-hospital; partially modifiable	If available: ensure protocol implementation
NIV/HFNO strategies: lack of availability, costs; reduced expertise, lack of personnel for safe implementation and monitoring	In-hospital; partially modifiable	If available: training to identify early failure; Ensure adequate monitoring for the need of endotracheal intubation
Molecular testing: costs, availability, adequate timing, and interpretation of test results	In-hospital; partially modifiable	If available: implement a process to guarantee timely results; interaction of microbiologists/infectious disease specialists

CAP community-acquired pneumonia, *HFNO* high flow nasal oxygen therapy, *ICU* intensive care unit, *NIV* noninvasive ventilation, *PCT* procalcitonin

follow the guidelines are also frequent issues that generate long evidence of practice gaps [55].

Focusing on the eight specific recommendations, we identify at least three that are particularly challenging to implement broadly. First, although molecular testing improves etiologic identification and accurate antimicrobial use, in certain regions, even standard microbiology testing is not fully available, and costs remain elevated. In addition, proper implementation of lab and clinical processes should be fostered to ensure short turnaround times and a correct interpretation of the results.

Procalcitonin remains expensive, making it relatively unavailable in low-resource settings, and when available, studies demonstrate that protocol over-ruling is frequent, significantly reducing the benefits of its use [56].

Finally, considering NIV and high-flow nasal oxygen (HFNO) therapy, although these strategies are safe and effective, the studies that demonstrated their benefits were mostly performed in HICs and in COVID-19 patients. Low-resource settings (apart from the limited availability of the devices [57]) may have difficulties in implementation due to insufficient or poorly trained staff. To safely implement these measures, the ICU team should be able to deliver constant surveillance and be trained to identify signs of failure. Staffing patterns and organizational factors play a major role in protocol and process of care implementation and may blunt the positive effects of treatments [58]. It is well-acknowledged that poor staffing patterns are associated with reduced adherence to protocols to prevent ICU-acquired complications leading to longer duration of mechanical ventilation, increased rates of ICU-acquired infections, and weakness [59–61]. In this scenario, the judicious use of adjunctive corticosteroids should be considered as they could potentially increase the rates of such adverse events when the standards of care are low.

In summary, the broad application of the guidelines internationally presents major challenges (Fig. 1) that requires an understanding of local contextual factors, a focus on standards of care and preventive measures as well as data originating from local research. Potential solutions to increase the broad applicability of the guidelines are in Fig. 2.

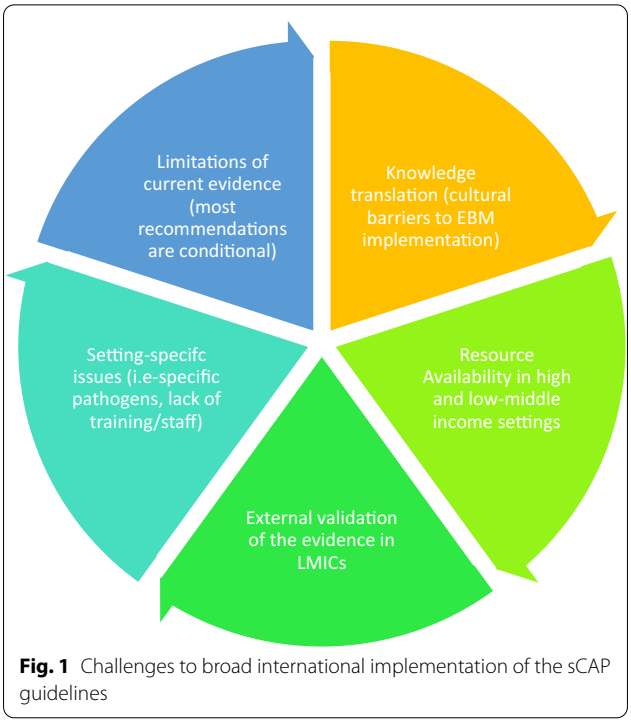
Limitations of current evidence (most recommendations are conditional)
Knowledge translation (cultural barriers to EBM implementation)
Resource Availability in high and low-middle income settings
External validation of the evidence in LMICs
Setting-specifc issues (i.e-specific pathogens, lack of training/staff)

Fig. 1 Challenges to broad international implementation of the sCAP guidelines

Research priorities

sCAP is still a deadly disease, and there are areas of improvement in research that need to be urgently considered [62, 63]. We can divide the need for research into three main categories: detection, diagnosis and resource allocation, antibiotic treatment and adjuvant therapy.

Regarding detection, molecular testing is one of the most needed research areas. The type of testing has important implications [64]. Traditionally, most tests were based on the amplification of pathogen DNA [65]. However, other technologies, such as fluorescence in situ hybridization (FISH), can theoretically improve specificity with lower sensitivity even in mycobacterium tuberculosis, a frequent cause of sCAP in LMIC [66]. Another area of great importance is the use of more advanced techniques, such as the next-generation sequencing (NGS) [67]; however, this technique needs to be validated in sCAP. One common problem with these techniques is how cost can be incorporated into healthcare systems. There is a need to analyze the absolute cost of such techniques and the relative cost when matching with antibiotic usage [68].

Biomarkers have always been the most desired tools for diagnosis and shortening antibiotic treatment [56]. The main problem in the past has been that companies have tried to use their biomarkers for all aspects of the infection. Some promising biomarkers are currently being discovered, but more importantly, it is to determine if they will be integrated into clinical trial designs [69].

New antibiotics have been launched over the last few years to treat resistant strains of *S. pneumoniae* and MRSA, but the area of more development is to treat some viral sCAP [43]. We have seen with COVID-19 how much a viral infection can damage the parenchymal lung tissue, and there is less investment in this area. We need effective new antivirals, more focused, to avoid the overuse of antibiotics when the diagnosis of a viral infection is clear.

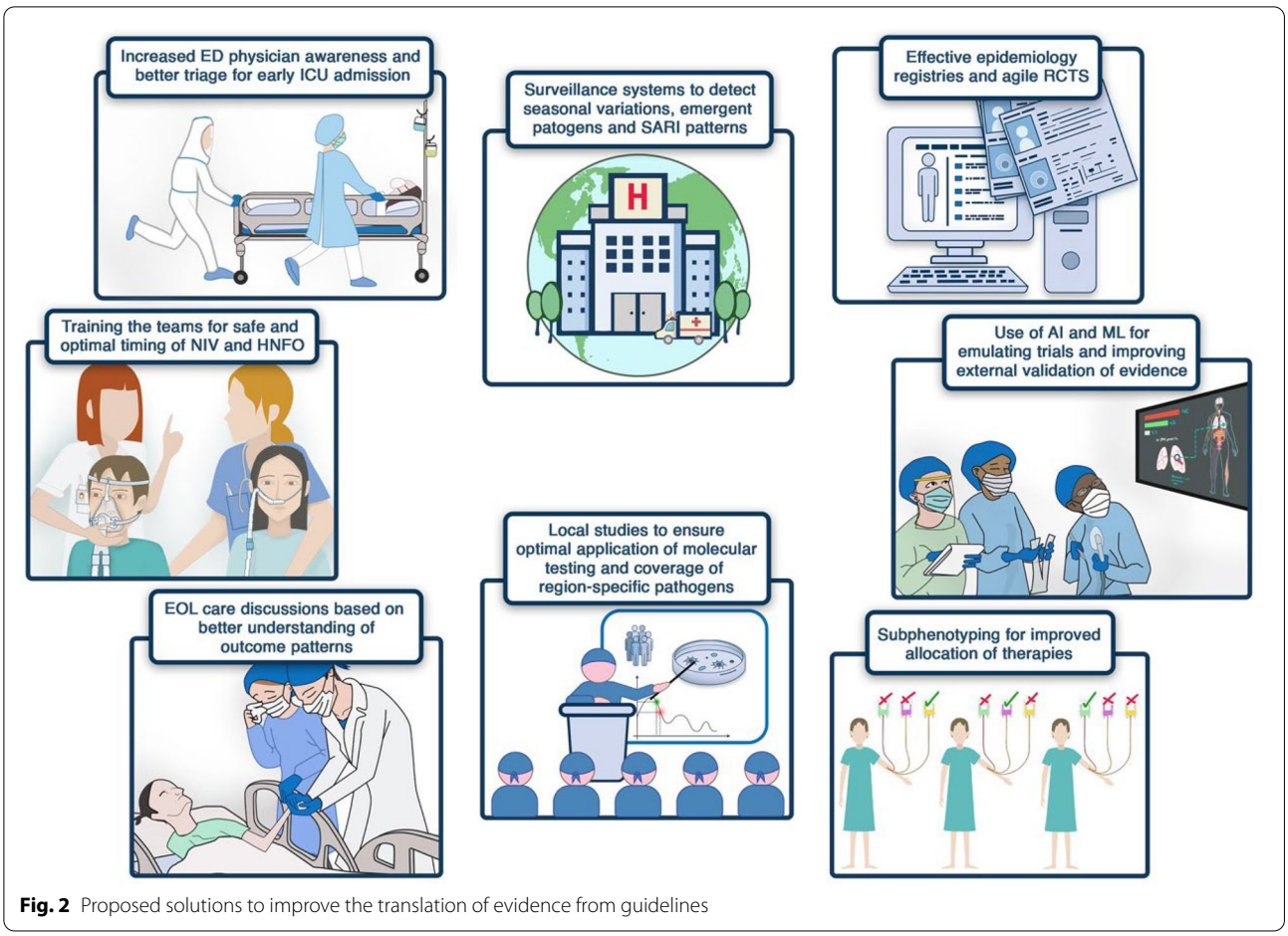
Increased ED physician awareness and better triage for early ICU admission
Surveillance systems to detect seasonal variations, emergent patogens and SARI patterns
Effective epidemiology registries and agile RCTS
Training the teams for safe and optimal timing of NIV and HNFO
Use of AI and ML for emulating trials and improving external validation of evidence
Local studies to ensure optimal application of molecular testing and coverage of region-specific pathogens
EOL care discussions based on better understanding of outcome patterns
Subphenotyping for improved allocation of therapies

Fig. 2 Proposed solutions to improve the translation of evidence from guidelines

Finally, after adequate antibiotic treatment, co-adjuvants are a step forward. There is more evidence of corticosteroids in patients with sCAP and septic shock, as recently recommended by the first published guidelines in severe forms of CAP [2]. But should we modulate the immune response with other agents? Understanding better the physiopathology and different clinical phenotypes of the patient would guide us in a personalized approach. Finally, from an implementation science perspective, future studies in different geo-economic settings are granted to evaluate both fidelity to intervention and effectiveness of the guidelines' implementation as a whole.

Conclusions

In summary, the recent guidelines mark a significant milestone in the management of severe community-acquired pneumonia (sCAP) patients, offering a comprehensive framework for healthcare practitioners. Our assessment reveals that substantial challenges persist in implementing these guidelines in LMI and LMIC. The hurdles of external validation, resource availability, and the necessity for setting-specific adaptation pose substantial barriers.

Acknowledging these challenges is pivotal as we move forward. Immediate actions must be taken to initiate external validation studies, ensuring the guidelines' applicability across diverse healthcare settings. Simultaneously, efforts to enhance resource allocation and distribution are imperative to facilitate the seamless integration of these guidelines into everyday clinical practice.

Looking ahead, ongoing research and collaborative efforts are essential to refine and adapt these guidelines for various healthcare contexts. By addressing these challenges head-on, we can pave the way for a more effective and universally applicable approach to managing sCAP. Ultimately, bridging the gap between guidelines and practical implementation is not just a necessity; it is an ethical imperative, ensuring that every patient, regardless of their location or resources, receives the best possible care.

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Declarations

Conflicts of interest
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